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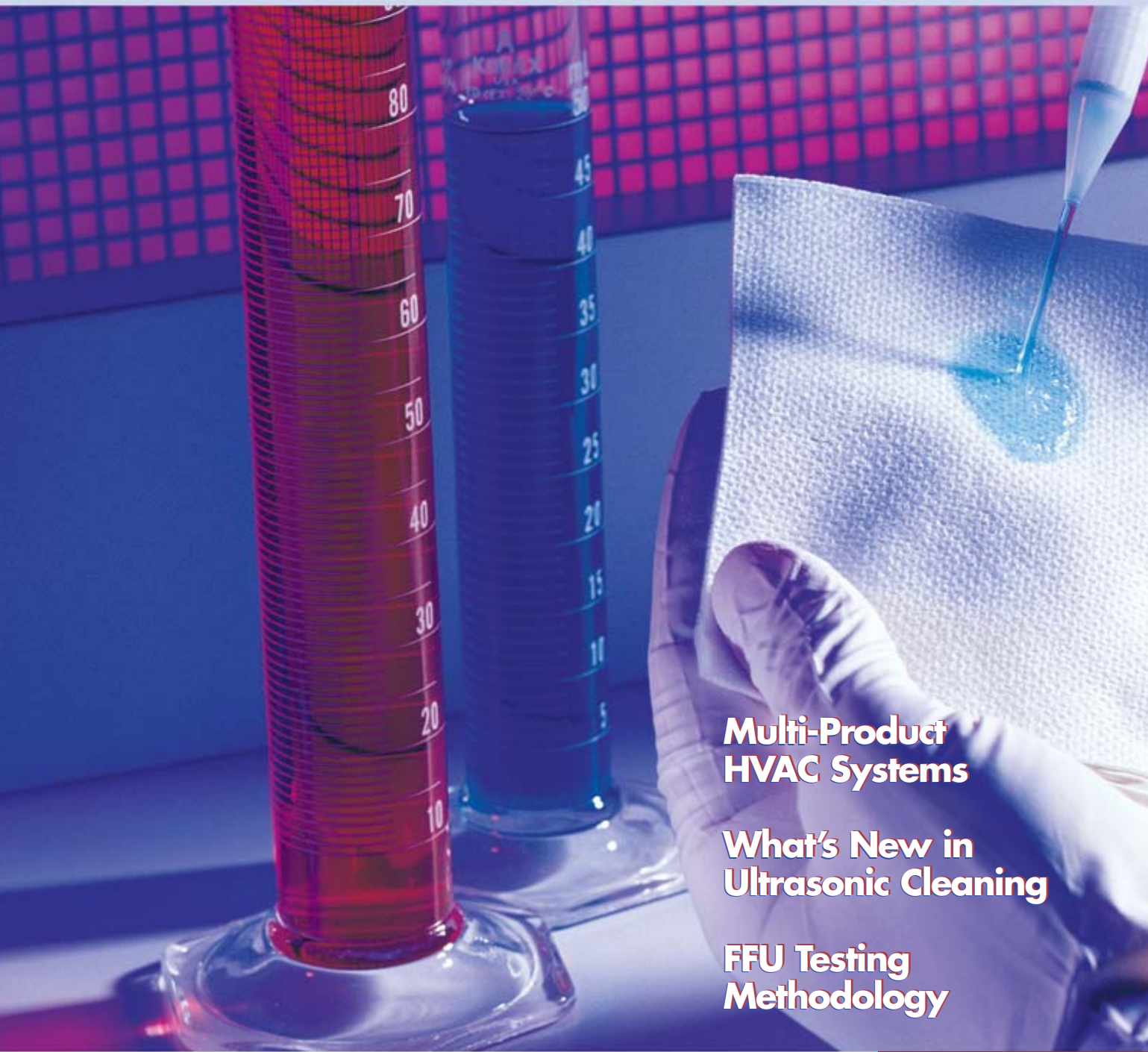
CONTAMINATION CONTROL • CLEANROOMS • CRITICAL ENVIRONMENTS

SEPTEMBER • 2004 VOL. 7 • NO. 9



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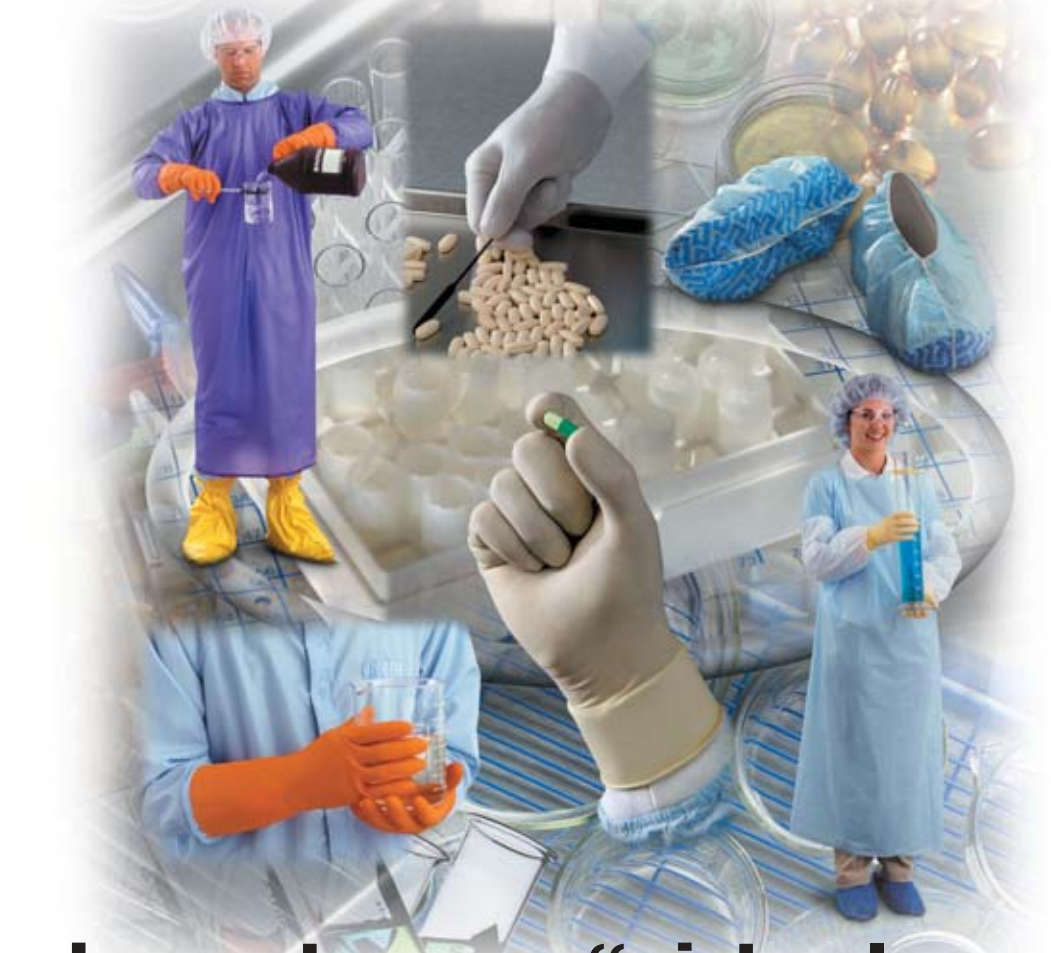

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POINT OF VIEW

GEOFFREY ROBINSON

The Difficulty of Keeping SOPs and Log Books/Sheets Simple

Although it is imperative in the particulate/viable contaminant control process that you address every detail, both large and small, there are times when an obsession with intricacy can make you your own worst enemy with regards to inspection, certification, and oversight agencies.

Governing bodies in our industry seldom mandate formats for SOPs or Log Books/Sheets. Often, terms such as "a system will be developed" or "a form for documenting will be instituted" are all you have as a guide. This puts the potential for contamination control cleaning system and documentation errors squarely in your lap.

Developing and implementing Standing (yes, it's "Standing," not "Standard;" most SOPs differ, making them non-standard) Operating Procedures, and forms to record the completion of a scheduled contamination control procedure, chemicals used, and completion time, etc. should be as "human being proof" as possible.

Words, and even punctuation marks, are potential disasters just waiting to happen. And they usually wait to happen when an oversight agency is on your property flipping through your SOPs and cleaning log books.

Keeping things simple can be extremely difficult when your training, experience, and background cry out for as much detail as you can possibly capture (there is guidance available for minimum information to be captured). But you should never lose sight of the fact that the more intricate (read that "cumbersome") you make a procedure, the more opportunity you create for error.

It doesn't matter whether you're in biotech, pharmaceutical, semiconductor, or the aerospace world, you need contamination control procedures and forms to record the timely and accurate completion of procedures. You need to ask yourself, with all the difficulties you face in the production of your final product, whatever that might be, is it necessary to make the contamination control process and its documentation more difficult than the manufacture of your final product?

> *"...the more intricate... you make a procedure, the more opportunity you create for error."*

Great speakers never lose sight of their audience's background, training, and makeup. The speaker's message is tailored for each audience's interest and comprehensive ability. Similarly, your SOPs and log sheets are filtered through the environment, education, background, and beliefs of its audience. Little difference exists between written and spoken instruction. Human beings make errors, but we are one of the only species capable of limiting the potential for error.

Whether you have an undergraduate degree or a PhD, it's a safe bet to assume that the staffers performing your contamination control procedures do not require the level of intricacy needed to produce your final product. If you have drafted a cleaning SOP and log sheet requiring scientific interpretation, you are your own worst enemy.

Note: Geoffrey Robinson will explain in detail the making of log books in a feature article appearing next month in A2C2.

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FRED NOWBAKH

HVAC DESIGN FOR MULTI-PRODUCT BIOPHARM MANUFACTURING

How the interrelation of processes and air handling units (AHUs) can produce an effective multi-product environment

In the past, many biotech companies chose the traditional approach of building a dedicated facility for the purpose of manufacturing a single product. This approach has some advantages from a cGMP/regulatory compliance, staffing and production control standpoint. However, this approach could put a heavy financial burden on established companies, as well as those start up companies with several products in the development pipeline who lack enough capital to support expenditure and investment in the construction of a new facility.

For several years it has become increasingly common for companies to develop multi-use manufacturing facilities capable of producing two or more products simultaneously. The multi-product or multi-use manufacturing nomenclature refers to a situation where a manufacturer of medicinal products produces two or more products within the same facility either concurrently or on a campaigned basis. Note that facility design for working with live cells vs. inactivated products needs to address strict containment issues for both personnel safety and cross contamination between areas and products.

In such facilities the following key factors are considered to minimize the chance of cross contamination between different production areas, and consequently the product:

- The engineering design
- Use of functionally closed process systems
- Air handling systems segregation
- Procedural separation of production activities
- Personnel flow, product flow, clean/dirty equipment flow
- Gowning regime
- Validated cleaning and changeover procedures

One of the key elements in a multi-product facility is the cleanroom design and its associated heating, ventilation and air conditioning (HVAC) system. A properly designed HVAC system will provide comfort, cleanliness, area segregation/containment, as well as personnel and product safety, which is essential for the successful operation of a multi-product biopharmaceutical manufacturing facility.

HVAC Design Considerations

The HVAC design of a multi-product manufacturing facility requires close interaction of the HVAC engineer, process engineer and the process architect (facility planner) from the start of the concept design throughout the completion of design documents. This will ensure implementation of an HVAC system in harmony with all elements of the facility as required for producing different products concurrently or on campaign basis.

This article will address the following key design considerations using an example of a multi-product facility, which was designed and validated successfully to produce multiple products with a campaigned manufacturing approach. The following requirements are defined during the project conceptualization phase.

- Area segregation and containment
- Product and personnel safety
- Temperature and humidity
- Area classification and pressurization
- Building automation system and environmental monitoring
- Regulatory requirements as it pertains to HVAC design

Area Segregation and Containment

An effective way to minimize cross contamination between different areas of processing operation is through area segregation of both process and cleanroom ventilation systems.

For cleanroom HVAC design, the area segregation is normally accomplished by using a separate air handling system dedicated to each area of the process operation including the inoculation suite, fermentation area, purification area (pre and post viral inactivation), and the bulk fill area. (See Figure 1)

Note that in this article, an air handling system consists of: air conditioning devices; air distribution ductwork and devices; supply; return; exhaust fans; and associated control systems.

The air handling system serving these areas could be a recirculating type or a once-through air design. The type of air handling system design and selection should be based on the type of product and process operation, as well as process equipment design (open vs. closed systems), product manipulation and toxicity of the product being produced.

As an example, when the potential of releasing dust or aerosolized materials from toxic substances and/or infectious agents into the room exists, utilization of a once-through HVAC system is recommended. This will protect the ventilation system serving the multi-use production area, and ulti-

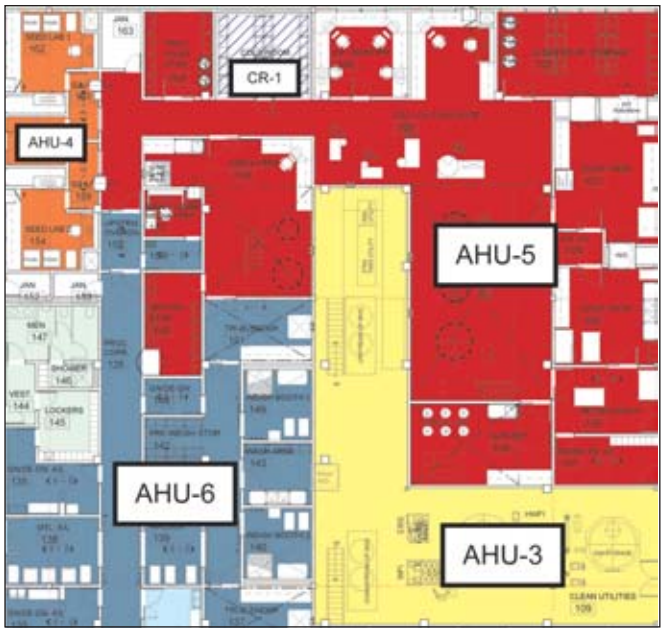

Figure 1. AHU Boundary (This facility had 9 AHUs.)

mately prevents cross contamination between products manufactured within the area by the ventilation system.

A dedicated air handling system for each area needs to be combined with airlock systems and a sound pressurization strategy to effectively control contaminated air from migrating into the adjacent zones housing different process operations.

In general, there are three basic airlock designs that can be combined or used individually to protect the cleanroom and/or prevent cross contamination between two adjacent areas of different process operations served by two different HVAC systems. These three airlock systems are:

- The cascading pressure airlock
- The pressure bubble
- The pressure sink

The cascading pressure airlock is used to protect clean areas from adjacent areas with lower required cleanliness. Normally, in this type of airlock, the transfer from the cleaner area, which does not pose any issue with cross contamination, is pushed into an access hallway. (See Figure 3)

The pressure bubble airlock is used to create a barrier between the cleanroom where the process resides and the adjacent area or access hallway. As the name implies, this type of airlock is a pressurized space that pushes the air out and into both the areas it protects. This type of airlock creates a barrier between the two spaces it serves, thus preventing cross contamination. (See Figure 4)

The pressure sink airlock is used to create a barrier between the cleanroom where the process resides and the adjacent area or access hallway. This type of airlock is a negatively pressurized space that pulls the air in from both the process area and the adjacent space thus creating a barrier between the two spaces it serves. (See Figure 4)

A combination of sink and bubble air lock design is also used for creating a barrier between potent compound or biocontained clean areas and the adjacent space.

Figures 1 and 2 show a facility designed and configured to manufacture the two different products "A" and "B" on a campaigned basis. By having HVAC and process systems segregated and dedicated to each stage of the process, the manufacturer was able to implement cleaning and changeover procedures to prepare the upstream manufacturing area for product "B," while maintaining the integrity and cleanliness required for downstream unit operations processing product "A." Note that this applies for segregation between live/dead cells and pre/post viral inactivation throughout the process operation.

As mentioned earlier, airlock and pass-through systems are utilized to segregate different production areas to achieve containment and reduce the chance of cross contamination between manufacturing areas.

Product and Personnel Safety

An appropriate cleanroom design addresses product safety by controlling both the number of viable and the non-viable airborne particles to an acceptable level for the process operation and associated cleanroom classification, as defined in the basis of the design during the project conceptualization phase. To protect the product from contamination, conventional cleanrooms are typically supplied with HEPA filtered air and local unidirectional hoods above areas where the product is exposed to the environment. Area segregation, as discussed earlier, would prevent cross contamination between two different products or product processing operations.

The personnel safety in areas handling raw material and/or working with live cells is achieved using containment hoods,

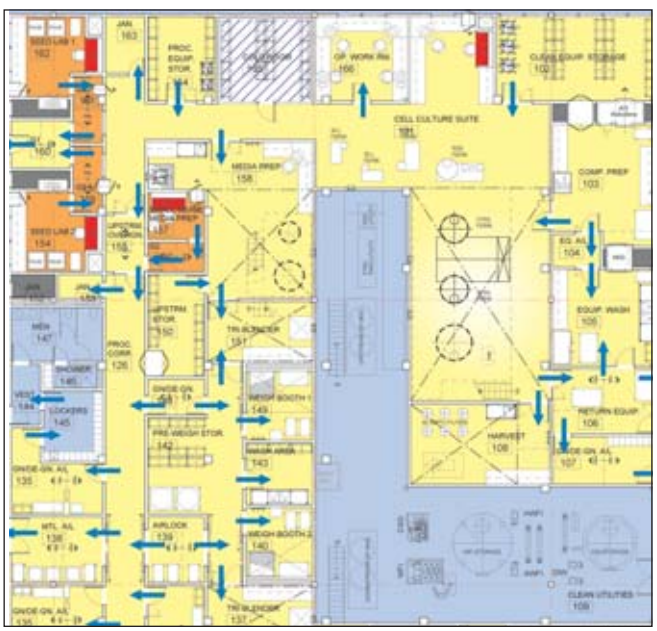

Figure 2. Pressurization and Classification *(For color key, refer to table 1, page 12)*

isolators, masks and SOPs, combined with proper facility design and layout. The containment device, custom or pre-fabricated, should be designed to minimize the chance of operator error in the handling of product, and the location should be incorporated into the cleanroom layout design such that the airflow patterns do not affect the containment device's performance and integrity.

Temperature and Humidity

The control of temperature and humidity within process areas is based on area cleanliness, product requirements and occupant comfort. These parameters should be defined and included in the basis of design at the early stages of the conceptualization phase.

For space temperature maintenance, reheat coils must be installed in the supply ductwork serving the space or cluster of spaces. The thermostat should be located within any areas having critical process operations and temperature requirements.

The temperature set point for comfort is usually 68°F or less depending on the required level of gowning for the personnel working in the process area.

Space relative humidity (RH) affects personnel particulate shedding (space cleanliness) if the RH is too low, and promotes the growth of toxic molds and other forms of biological contaminants when too high. RH could also be detrimental to hydroscopic powder materials that are sensitive to high moisture content in the ventilation air, which causes clogging of powders used in buffer and media preparation.

For products and processes that require a specific range of relative humidity, the HVAC system should have the capability of providing both humidification and dehumidification to maintain the space RH within the pre-determined range. A relative humidity range of 30% to 60% would work with most products and provide a comfortable working environment for gowned personnel.

For humidification, a clean steam humidifier is recommended. The steam humidifier can be installed at the AHU to maintain an average humidity setpoint for areas served by the air handling system. However, if humidification control for a specific processing area is required, then a duct-mounted humidifier should be used to maintain that space humidity requirement.

Dehumidification can also be accomplished by using the air handling unit cooling coil if the plant's chilled water temperature is low enough (40-42°F) to extract moisture from the supply air. Note that the cooling coil face velocity should be between 400 to 450 ft/min to improve the cooling coil moisture extraction. If the process operation requires a higher level of dehumidification that cannot be attained with cooling coil dehumidification, then a dry or wet type dehumidifier should be used.

Selecting an appropriate location for the humidistat is important for maintaining the design setpoint. Designers working with end users should determine the level of average RH for an area served by the air handling unit vs. one specific space or area. To maintain RH for process areas served by an AHU, the RH sensor can be located in the supply main or return main of the AHU. But for individual space RH control, the sensor should be located in the space or the common return/exhaust duct serving that space.

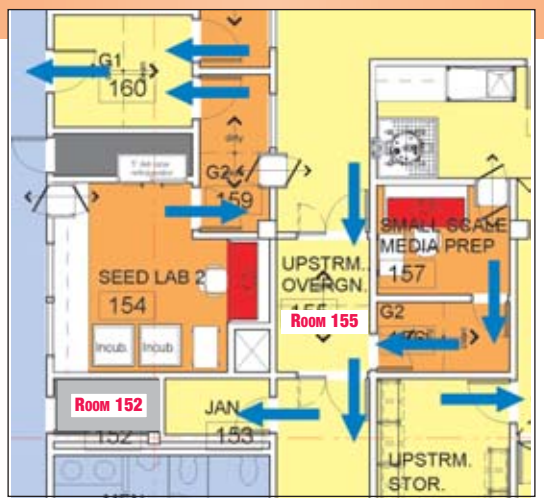

Figure 3. Cascading Pressure Airlock (Rooms 152 and 155) *(For color key, refer to table 1, page 12)*

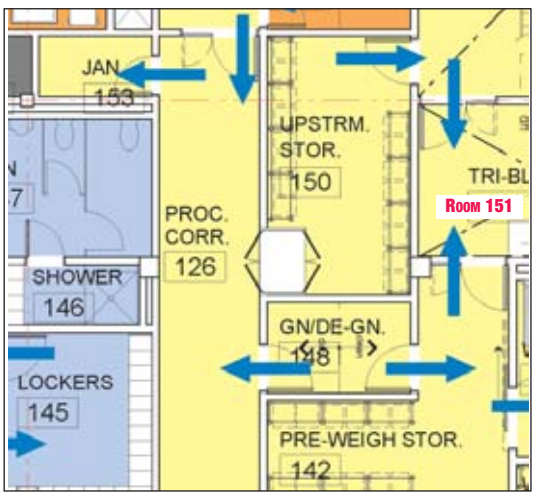

Figure 4. Pressure bubble or positively pressurized A/L (Room 151) *(For color key, refer to table 1, page 12)*

Area Classification and Pressurization

The process operation dictates the area classification or cleanliness of the environment in which the product is produced, purified and filled. Normally, upstream processes require lower area classification while the processes are exposed to the surrounding environment; down stream manufacturing steps require a higher area classification in order to protect the integrity of the bulk product that is in the final state ready for shipping to the fill and finish facility. All classified area ventilation should be supplied through terminal HEPAs and returned/exhausted through low wall grilles. The HEPA filtration for ISO9/Grade D areas could be installed inside the air handling unit and the return/exhaust grilles could be ceiling mounted. (See Figure 2)

The various classifications require a different number of air changes per hour (ACH) to achieve the required cleanliness associated with the class or grade designation. Typically, 20 air changes per hour is the starting point for ISO 8/Class 100,000 process areas. This ventilation rate (ACH) could be higher depending on the nature of the process and number of

personnel present. Higher classifications require higher ACH and the ISO5/Class 100 is defined based on air velocity of 90 (+/-20%) feet per minute.

The area classifications most commonly used in the biotech industry are shown in Table 1. Some companies use ISO6/Class 1000 for the background in the critical areas with local ISO5/Class 100. The first column in Table 1 is a cross reference to the old standards 209E. Note that on November 29, 2001 Federal Standard 209E was canceled and superseded by ISO 14644-1 and 14644-2.

Rooms where the most critical processing takes place should have the highest differential pressure with respect to

Table 1. EU and ISO Environmental requirement comparisons

FEDERAL STD 209E Max # of Particles per ft^3 (0.5 µm and larger)	Max # of Particles per ft^3 (0.5 µm and larger)	Max # of Particles per m^3 (0.5 µm and larger)		ISO	EU
	In Operation	At Rest (EU)	In Operation (ISO / EU)		
Class 100	100	3,500	3,520/3,500	ISO 5	Grade A
Class 100	100	3,500			Grade B
Class 10,000	10,000		352,000/350,000	ISO 7	Grade B
Class 10,000	10,000	350,000			Grade C
Class 100,000	100,000		3,520,000/3,500,000	ISO 8	Grade C
		3,500,000	35,200,000/Not Defined	ISO 9	Grade D

1. For ISO the particulate size and operational state (as built, at rest, or in operation) shall be defined
2. Note that EU and ISO particle counts are slightly different, e.g. 3,250 vs. 3,500 for ISO/Grade B and so on.
3. Above colors (Red, Orange and Yellow) are used in Figure 1, 2, and 3 to identify area classification in operation.

the areas surrounding the process suite. Overall the designer should maintain the building positive with respect to the outside of the building.

The pressure cascade should be designed such that the areas with the most critical processing have the highest pressure and the less critical areas have lower pressurization by a pre-determined pressure differential in the order of cleanliness required for each stage of process operation. Pressure drop across the airlocks separating two different classifications should be 0.05" of Water Column (W.C.) for US and between 10 to 15 Pascal (0.04" to 0.05" W.C.) in compliance with EU requirements. The least critical areas, like common corridors and staging areas, should have the lowest pressurization while maintaining the positive pressurization with respect to the outdoor environment. Determining the required space pressurization for cascading and/or regulatory requirements, the designer should carefully consider the pressure levels in the adjacent rooms to prevent possible problems with the door opening/closing due to excessive pressure differential across the doors.

Building Automation System and Environmental Monitoring

The facility's building automation system (BAS) requires the ability to monitor and control the setpoints as determined by the design team and documented in the project basis of design. The BAS must be capable of indicating and recording alerts and alarms when the critical processing space's temperature/humidity/pressurization is not to specification.

Note that data recording by BAS and or other means should be in accordance to cGMP requirements and of a methodology acceptable by the regulatory agencies.

Temperature and RH sensors should be installed in the critical processing rooms, cold rooms, warm rooms and in the HVAC equipment serving the critical manufacturing areas to monitor the system's performance as required in the basis of design and validation documents.

Regulatory Requirements As It Pertains To HVAC Design

The design and construction of multi-product manufacturing facilities shall meet cGMP in compliance with the FDA and, if exported, the regulations for the country in which the product is marketed and sold to the consumer.

The basic requirements for US regulations are found in the Code of Federal Regulations (CFR), Title 21, Part 210, 211, 606-680 and 820.

Part 210 covers cGMP in manufacturing, processing, packaging, or holding of drug products and Part 211 covers cGMPs for finished pharmaceuticals.

On November 29, 2001, the General Service Administration issued a notice that "Federal Standard 209E dated September 11, 1992 is hereby cancelled and superseded by International Organization for Standardization (ISO) standards for cleanrooms and associated controlled environments.

- ISO 14644-1 Part 1 (Classification of Air Cleanliness)
- ISO 14644-2 Part 2 (Specifications for testing and monitoring to prove continued compliance with ISO 14644-1)."

European Community GMPs could be found in the "Rules and Guidance for Pharmaceutical Manufacturers and Distributors, 2002."

Conclusion

The material covered in this article establishes the fact that a successful design, construction and operation of a multi-product facility depends on the interrelation of the manufacturing procedures, process and process equipment design, cleanroom and associated HVAC design, equipment flow, material flow, personnel flow, building design, validated cleaning and changeover procedures.

Several key factors for design of HVAC systems for a multi-product manufacturing facility were discussed. The implementation of these design considerations, and the adherence to cGMP regulations with a well-designed building layout will serve as basis for a successful multi-product facility.

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CONTINUING DEVELOPMENTS IN ULTRASONIC TECHNOLOGY

The options for ultrasonic technology have expanded from a few frequencies to a plethora of "frequency strategies" helping to improve cleaning and reduce part damage

Ultrasonics, the sound you cannot hear, has emerged as a valuable tool in achieving the cleanliness required by today's ever-advancing technology. Disc drives, silicon wafers and chips, medical implants, and all sorts of critical hardware require ultrasonic cleaning to function properly—or at all. Traditional ultrasonic equipment operating in the 20 to 40kHz range served well for most of 50 years. Prior to the 1980s, ultrasonic technology was essentially "mature" with periods of excitement provided only by the occasional advancement in transducer and/or generator technology initiated by the availability of new fabrication materials for transducers and electronic devices; this improved the efficiency and reliability of generators. This period also saw the advancement of the increasingly affordable ultrasonic technology into more and more "industrial" applications including plating, surface finishing and metal fabrication.

Starting in the 1980s, however, a new "wave" of ultrasonic technology development was initiated as ultrasonic manufacturers began to expand the envelope of available ultrasonic parameters. One cannot be sure if the technology preceded the need or if the technology was prompted by need, but in any event, things started happening. Ultrasonic technology began to move forward and with this motion came a flurry of "position jockeying" by the handful of primary ultrasonic suppliers.

Ultrasonic Generator Technology

Sweep Frequency

The first major generator development was sweep frequency. Ultrasonic cleaning had long been troubled by the formation of standing waves which, under the right conditions, could produce parts with "zebra stripes." These stripes were created as the reflecting sound wave fell back on itself and reinforced its intensity in horizontal zones located approximately one half wavelength apart. At best, one saw these bands as areas of cleaning vs. non-cleaning on the surface of the part. At worst, parts, especially those fabricated from softer metals including aluminum, brass and copper, were actually etched by high ultrasonic intensity in the areas of reinforcement. A simple solution to this problem was to move parts vertically through the ultrasonic field to spread out the high intensity effect by scanning the part.

It was discovered that varying or "sweeping" the ultrasonic generator frequency over time effectively broke up the standing waves and reduced the tendency for zebra striping to occur. It was assumed that since the spacing of the stripes was based on frequency, formation of damaging standing waves relied on a fixed ultrasonic frequency. Varying the ultrasonic frequency slightly up and down would cause movement of the bands of high intensity. The effectiveness of sweeping frequency in reducing zebra strips was demonstrated repeatedly when the rate of sweeping and the bandwidth of sweep frequencies were designed to prevent resonance of the liquid column.

Another effect of sweeping went almost unnoticed. Ultrasonic transducers of the time were all relatively "High Q" devices. In simple terms, like a tuning fork, they operated well at their resonant frequency, but as the driving frequency was changed, performance deteriorated rapidly. Sweeping the ultrasonic frequency attempted to drive the transducer at a frequency somewhat off its resonant frequency during most of the sweep cycle. This effort effectively reduced the output power of the transducer without an apparent reduction in the power delivered from the ultrasonic generator. Interestingly, a reduction in ultrasonic output power was also shown to reduce the zebra striping effect.

In defense of sweep frequency, most ultrasonic transducers consist of an array of individual driving elements (also sometimes individually called transducers). Despite the considerable effort given in manufacturing to assure that these individual elements all operate at the same frequency, there is always a slight variance in frequency of the elements in any transducer array even if they are individually chosen and matched prior to bonding to the tank. When a transducer array is operated at a single, fixed frequency, the individual elements (which are wired in parallel), are forced to divide up the available power. Elements with resonant frequencies closest to the frequency provided by the ultrasonic generator will draw the largest portion of power and therefore provide the highest ultrasonic intensity. Meanwhile, elements operating off their resonant frequency will have reduced output. The effect is non-uniformity of the ultrasonic field.

With sweep frequency, each transducer element sees its preferred driving frequency twice during each sweep cycle (provided it is within range of the sweep). The result is that a much more uniform ultrasonic field is produced in the cleaning tank. In addition, the use of sweeping frequency provides more useful cavitation per watt of ultrasonic excitation as a larger bubble population is resonated as the frequency varies. These are undeniable benefits of sweep frequency ultrasonics.

Extensions of sweeping frequency technology include varying the bandwidth and frequency of the frequency sweep itself. In some cases the sweep is randomized to eliminate the potential for damaging resonance effects that may be created as a result of the sweep frequency itself. These enhancements have found value in applications where both delicate and seemingly robust components are prone to fatigue failure when excited at their resonant frequency.

Pulse

Within the same time frame as the development of sweep frequency, "pulse" was identified as an important parameter in ultrasonic cleaning. In simple terms, pulse means turning the ultrasonic energy on and off. Variables are duty cycle (percentage of ON time), frequency of the repeating on-off cycle, and pulse amplitude. Although it would at first seem counter-intuitive to better cleaning to turn off the ultrasonic power for a portion of time, this action does result in better cleaning results. The reason is that there is a burst of high energy ultrasonic power generated each time the ultrasonic power is turned on, which occurs before the cavitation bubble field reaches saturation. During this time, sound passes quite freely through the liquid without being attenuated by the saturated cloud of bubbles which are released by the sound field after the ultrasonic energy is initiated. This effect is familiar to those who have witnessed ultrasonic energy in some very low surface tension solvents. Droplets of solvent are often driven several inches high during the initiation of cavitation in a solvent.

The impact of the recognition of this effect was somewhat softened when it was

realized that most ultrasonic cleaning systems at that time already had some inherent degree of pulse at twice the power line frequency as a result of a one half wave rectified power supply. Many manufacturers, in fact, adjusted the duty cycle of this inherent pulse as a means of providing a form of "power control." Pulse, by the way, should not be confused with "degas." The degassing cycle uses considerably longer time periods to allow gas bubbles, formed as the result of cavitation, to float to the surface of a liquid prior to re-applying ultrasonic energy. Pulse usually means 50 to 150 on-off cycles per second while degas uses a cycle time up to several seconds between pulses. The effect of pulse is most pronounced in solvents but can also be seen in aqueous solutions.

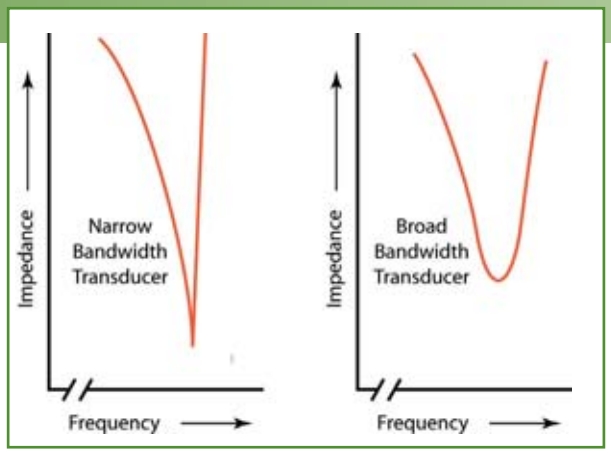


Figure 1. Narrow bandwidth vs. broad bandwidth.

Waveform Flexibility

In its simplest form, an ultrasonic generator is nothing more than a frequency converter. Just as a rectifier changes alternating current to direct current, an ultrasonic generator changes electrical energy at the power line frequency to electrical energy at the frequency required to drive the ultrasonic transducer.

Ever-advancing electronic technology has given designers of ultrasonic generators the tools to allow them to customize generator characteristics not limited to sweep and pulse. Today, nearly any imaginable wave characteristic can be customized (using techniques much like those used in musical synthesizers). Ultrasonic frequency and amplitude can be modulated instant by instant. Waveform patterns can be programmed or randomized depending on each individual application. Research continues to explore and define the proper use of all of these waveform parameters.

Transducer Technology

Many of the developments in ultrasonic generator technology were driven at least in part by developments in ultrasonic transducers. Transducer technology has advanced notably over the past several years.

Transducer Bandwidth

Ultrasonic transducers are typically designed to resonate at their operating frequency. Much like bells and tuning forks, however, they are less efficient when driven at a frequency even slightly different than the one at which they were intended to operate. The impedance vs. frequency characteristic of a resonant device expresses its sensitivity to frequency. The deeper and sharper the resonance, the more selective the device is to frequency. Figure 1 shows the impedance vs. frequency curves for a transducer with a narrow bandwidth and a transducer with a broad bandwidth.

Classical transducer technology would favor sharper and deeper resonance, as shown in the graph on the left in Figure 1, for a transducer designed to operate at a single, fixed frequency. Ultrasonic transducers, providing sharp resonance, provide high efficiency output and the feedback required to allow feedback loops that control and automatically adjust generator frequency in real time in response to the characteristics of changing loads.

The development of frequency sweep technology, therefore, presented a bit of a technical conundrum. Sharply resonant transducers suffer a significant reduction in power output when driven by an ultrasonic generator providing sweep frequency. In fact, maximum efficiency is only achieved at the instant the driving signal equals the resonant frequency of the transducer (twice every sweep cycle). Maximizing the effectiveness of sweeping frequency prompted the redesign of ultrasonic transducers to provide a wider frequency acceptance. Figure 2 shows one benefit of a wider bandwidth transducer.

Higher Frequencies

Prior to the early 1990s there was a notable gap in the utilized ultrasonic spectrum. This gap was bordered by the highest ultrasonic frequency (something just short of 100kHz) and the frequencies near 1mHz used for megasonic cleaning. It is generally agreed that megasonic cleaning is based on the phenomenon of acoustic streaming, which is a somewhat ➤

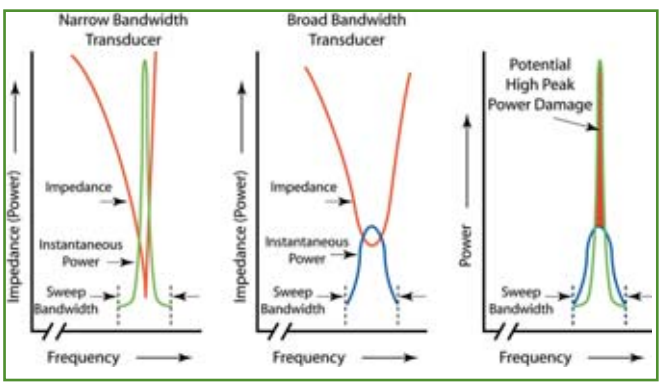
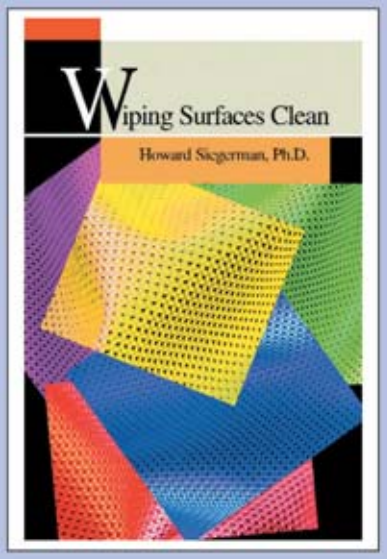


Figure 2. The two graphs on the left show power curves resulting from narrow and broad band transducers. The area under the power curve represents total delivered power. Although the area under the curve is the same in both examples, the narrow band transducer may produce high peak power as shown at the right, which may potentially cause damage to delicate substrates.



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different mechanism than that of cavitation, which is associated with ultrasonic cleaning. Acoustic streaming does not necessarily involve the formation and violent collapse of cavitation bubbles. Megasonic technology is also a more "line of sight" phenomenon than cleaning using cavitation.

This frequency gap started closing when the removal of micron and sub-micron sized particles became important. Increasing frequency has two effects that are beneficial to the removal of small particles. Higher frequencies produce smaller cavitation bubbles that are able to produce a force normal to the substrate of sufficient magnitude to dislodge and remove very small particles. In addition, the thickness of the "boundary layer" present at the interface between a liquid and a substrate is reduced at higher frequency. Within the boundary layer, it is difficult or impossible to produce the relative shearing forces required to remove particles. Reducing the thickness of the boundary layer provides access to smaller and smaller particles for removal.

The operating frequency of a transducer is determined by its geometry. In general, a shorter transducer (just like a shorter tuning fork) will operate at a higher frequency. However, by utilizing harmonics, transducers of varying size can be designed to operate at a frequency other than that established by length alone. In any event, transducers became available that would operate at frequencies above 100kHz. These transducers quickly found favor in systems where the removal of very small particles was of primary importance. This area of cleaning was quickly dubbed "precision cleaning." The frequency spectrum continues to grow, now having reached 300kHz. The benefit of higher frequency in the removal of small particles is well established. The down-side of higher frequency is that larger particles are often too well attached to be removed by the more gentle force provided by the implosion of smaller cavitation bubbles produced at higher frequencies.

Multiple Frequencies

The effectiveness of higher ultrasonic frequency for removing small particles has been demonstrated. Higher frequencies, however, may not provide cavitation implosions with sufficient energy to dislodge and remove larger particles. In fact, a given frequency will most effectively remove particles falling within a given size range.

The removal of a wider range of particle sizes can be achieved in one of two ways. Increased ultrasonic power at a single frequency may provide sufficient energy to remove particles in a broader size range. The risk of this approach is damage to the substrate as a result of extremely high power.

The other approach is to use multiple ultrasonic frequencies each of which removes particles in a targeted size range. A series of cleaning tanks operating at a discrete frequency can do this.

Continuing ultrasonic transducer development now offers ultrasonic transducers that resonate at more than one frequency. These multi-frequency transducers, used in conjunction with a digitally controlled multi-frequency generator provide the ability to remove particles with a wide range of sizes in a single process tank.

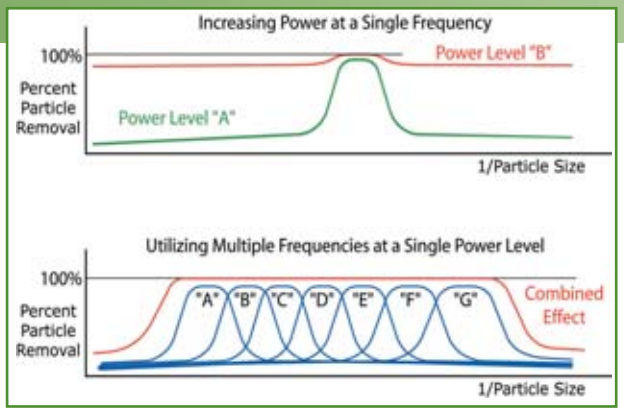

Figure 3. The upper illustration shows the effect of increasing power to increase the range of particle sizes removed from a substrate. This may require power levels sufficient to cause damage to the substrate. The lower illustration shows the use of several frequencies, A, B, C, etc., each at lower power to provide removal of a wide range of particle sizes without risk of damaging the substrate.

Application

The options for ultrasonic technology have advanced from a few, set frequencies to a veritable "orchestra" of inaudible sound. Some of the advancements described above were developed in response to clearly defined needs such as improving the uniformity of cleaning or eliminating part damage due to induced resonance. Others are natural extensions of developing technology and, although available, do not yet have a clearly defined use.

Although cleaning has always been a primary target application for high power ultrasonic technology, new uses are being developed for growing ultrasonic technology as this article is written. De-agglomeration and particle size refinement of CMP slurries, micro-finishing of surfaces to change or enhance surface characteristics, applications in liquid particle counting, enhancement of plating and other deposition processes, and a multitude of other new developments are either at or nearing production stage.

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Session 1: INTRODUCTION TO CLEANROOM TECHNOLOGY

Familiarity breeds contempt. The cleanroom of 20 years ago was a new creature. An elite handful of specialty contractors made a living consulting with end users, designing and building clean facilities, and certifying that the facilities were in fact, clean. Today much of the mystique is gone. The "cleanroom" is old hat. Yet interestingly we continue to see cleanrooms that aren't clean, that don't meet end user expectations, and that must undergo retrofit before they function as intended. This half day presentation revisits the basics and provides a necessary cleanroom design foundation to the practitioner of the 21st century. Topics include; why cleanrooms don't work; defining the cleanroom contractually and functionally; political considerations; design considerations; health sciences vs. microelectronics issues. One segment of the presentation will be devoted to a step by step design exercise to develop a conceptual design of a 2000 sq ft Class 1000 (ISO 6) generic cleanroom. This is a working session intended to confront attendees design issues and provide alignment for cleanroom designers and clean facility owner/managers.

Raymond K. Schneider, P.E., Cleanroom and HVAC Consultant, Practical Technology

Session 2: WHY CHOOSE A DESIGN/BUILD CONTRACTOR?

A design/build (D/B) contractor can expand your options because multiple contracts and relationships are not required. D/B contractors are vertically integrated and offer cost-effective solutions. A D/B contract means dealing with one source from start to finish and is an effective vehicle because one phone call puts you in touch with the single-source responsible party. Topics covered will include: feasibility studies, D/B definitions, plan and specification, D/B benefits, and what to watch out for.

David Kirkpatrick. P.E., Director of Engineering, Western Environmental Corporation

Session 3: LET THE BUYER BEWARE: A GUIDE FOR PROCUREMENT OF NEW, REFURBISHED, AND USED PROCESS TOOLS

This presentation will discuss the various pitfalls that exist in procuring process tools and suggested actions that can be taken to prevent misunderstandings, miscommunications, and contractual difficulties. Requests for proposals and quotations (how to write an effective one that clearly defines ALL your requirements), negotiating the deal, purchase orders, obtaining clear fit - up requirements (this is harder than you think), acceptance testing (both factory and site acceptance), crating and shipping and receiving will be covered. For refurbished and used tools, the presentation will discuss the lack of industry wide standards for tool decommissioning, storage, refurbishment, upgrades, and cleaning and the potentially serious impact that this may have when procuring tools from these sources.

Stephen Beck, Director of the Project Solutions Group, LeChase Construction

Session 4: DO'S AND DON'TS OF LAB EQUIPMENT IN NANOTECHNOLOGY IN RESEARCH FACILITIES

As we move into the research and/or manufacturing aspects of Nanotechnology, there is an ever-increasing landscape of facilities in the public and private sector being constructed to support these efforts. Watching and reviewing some of these projects, we have recognized an alarming absence of due diligence for the systems and components being installed to support them. Everyone understands the need for some level of controlled environment. This is especially true in the areas of contamination control. What seems to be missed is that many of the installations did not take into account the need to review materials of construction for the basic components being used in these facilities. It is the intent of this paper to provide advise on what to look for and why. In doing so, we hope to prevent the loss of contamination control which could prohibit the success of your projects.

Stephen L. Yellin, Group Director Advanced Technology, Lockwood Greene, Inc.

THURSDAY, APRIL 7, 2005

Morning

Registration and Breakfast	7:45- 9:00
Trade Presentations	8:00- 8:30
Session 1	9:00- 9:50
Session 1 cont'd	10:00- 10:50
Break	10:50- 11:20
Session 1 cont'd	11:20- 12:10

Afternoon

Lunch	12:15-1:45
Trade Presentations	1:15-1:45
Session 2	1:50-2:40
Break	2:40- 3:10
Session 3	3:10- 4:00
Session 3 cont'd	4:10- 5:00
Cocktail Party	5:15- 7:00

Session 5: CONVERTING AN EXISTING LAB SPACE INTO AN APPROVED BSL3 BIOSAFETY LAB

The basics of BioSafety design are well established in the CDC/NIH BMBL 4th Edition and associated guidelines, however the intricacies of interpreting the detail and converting your lab space into an approved BSL3 facility is not as clearcut as it may seem. Delegates will be taken through a typical single Lab BSL3 facility where some of the key pitfalls will be identified with appropriate strategies to deal with them. This session is for those professionals who have embarked on a BSL3 project and want to know what is not detailed in the guidelines; it will also offer a practical Design/Build guideline to getting your BSL3 facility approved.

Conor Murray, B.E. Elec, MIE, Technical Director, Ardmac Ltd.

Session 6: ENERGY MANAGEMENT OPPORTUNITIES IN CLEANROOMS: AN OVERVIEW OF R&D SPONSORED BY THE CALIFORNIA ENERGY COMMISSION

Cleanroom facilities offer an important (and often under-exploited) potential for energy savings. In California alone, electricity demand equivalent to the output of two large electric power plants could be avoided with the widespread adoption of measures to improve energy efficiency while saving half a billion dollars per year for facility owners. This presentation provides an overview of relevant work underway at Lawrence Berkeley National Laboratory (LBNL). Topics include: energy benchmarking, a standard for testing and reporting fan-filter unit energy performance, minienvironment efficiency assessments, demand-controlled filtration (controlling airflow based upon particle counts), and other resources such as a Cleanroom Programming Guide and a Design Intent Tool that facilitate inclusion of energy efficiency considerations in cleanroom design.

Bill Tschudi, Principal Investigator, Lawrence Berkeley National Laboratory

Dr. Tengfang Xu, PE, Project Manager, Environmental Energy Technologies Department, Lawrence Berkeley National Laboratory

Session 7: CLEANROOM PROCESS SYSTEMS FOR MICRO AND PHARMA FACILITIES

Why do we need Cleanrooms? Sometimes we forget that the Process is a key driver for most cleanroom space needs. The Cleanroom Shell is only one step in the programming of Cleanroom facilities. While the process infrastructure is one of the final steps of Cleanroom Construction, it is an essential first step in planning and programming a Cleanroom Facility. To provide the best-suited system, it is essential to develop the necessary understanding of the end user requirements for the manufacturing process. The Process Systems Infrastructure and Components require forethought, programming, planning, and proper selection of materials and equipment to meet the needs of the end users. Topics covered will include Process Systems Programming, Design Considerations, End User Expectations, Types of Systems, Developing Matrices of Process Tools, Sizing Process System Capacities, Materials Selection, Base-Build vs. Fit-up Considerations, Micro vs. Life Sciences Considerations, Life, Health & Safety Considerations, Environmental Considerations, and Ultimately Flexibility for the Future. The program is intended to provide a baseline overview for Cleanroom Process System Infrastructure to enable users to adapt a team approach for programming the process infrastructure for new cleanroom construction and/or retrofit to existing facilities.

William W. Johnson, Technical Sales Manager, Luwa USA

Jennifer Varnau, Process Systems Manager, Luwa USA

Brad Carr, Vice President - Sales and Marketing, Luwa USA

Ingo Stammitz, Business Development Cleanroom Technology (CRT) Luwa

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FOR MORE INFORMATION

For more information on the 2005 TurnKey Conference, go to www.a2c2.com or contact Mary Williams at mwilliams@a2c2.com; 603-672-9997 x113. For exhibit information contact Patrick Murphy at pmurphy@a2c2.com; 603-672-9997 x106.

FRIDAY, APRIL 8, 2005

Morning

Registration and Breakfast	7:45- 9:00
Trade Presentations	8:00- 8:30
Session 4	9:00- 9:50
Session 4 cont'd	10:00- 10:50
Break	10:50- 11:20
Session 5	11:20- 12:10

Afternoon

Lunch	12:15- 1:15
Session 6	1:20- 2:10
Break	2:10- 2:40
Session 7	2:40- 3:30
Session 7 cont'd	3:40- 4:30

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TENGFANG XU

INTRODUCING A STANDARD TESTING METHOD FOR FAN FILTER UNITS

A testing methodology for evaluating fan filter units' energy and air movement performance in a laboratory setting

Cleanroom HVAC systems, especially those requiring fan filter units (FFU) for recirculating air, typically account for a large portion of energy use in cleanrooms. Performance of HVAC systems varies significantly from cleanroom to cleanroom largely because of various factors, such as contamination control requirements, air handling unit designs, air system resistance, and efficiency levels offered by system components.[1] The studies described not only uncovered energy-saving opportunities in many cleanroom applications, but also indicated that optimizing aerodynamic performance in air recirculation systems appears to be a useful approach to improve energy efficiency in cleanrooms.

Because of their ease of installation, adaptability, and specific contamination control schemes, FFUs are being used more and more in air recirculation systems in cleanrooms. The large number of small fans can consume considerable energy in providing air recirculation. Therefore, understanding the performance of FFUs is important and can help to promote best practices in cleanroom design and operation. To date, typical manufacturer's data sheets usually contain claims that are seemingly similar; however, they usually do not reveal test methods, if they exist at all. Furthermore, statements of performance data that include power, airflow, and sound are commonly vague and could be misleading. In recent years, industries have shown growing interest in having a uniform method for testing and reporting FFU performance. Lawrence Berkeley National Laboratory (LBNL) is performing research to improve energy efficiency in contamination control facilities such as cleanrooms. The project goal is to develop a standard testing method for evaluating the performance of an FFU.[2]

This article describes the activities that LBNL has led in developing the standard for FFUs' energy performance. It also summarizes results of laboratory-measured performance of 20 fan filter units (FFUs) tested by Industrial Technology Research Institute (ITRI).[3,4]

Partnerships

This procedure is intended for industry use, including fan filter unit manufacturers, end users, utility companies, and designers. During the development of the standard procedure for testing FFUs' energy performance, we have built strong partnerships with these industry stakeholders and other industry associations. The key partners include:

- California Energy Commission (CEC) and California utility companies
- Industrial Technology Research Institute (ITRI), Taiwan
- The Institute of Environmental Sciences and Technology (IEST)
- Air Movement and Control Association International (AMCA)
- SEMATECH International
- Suppliers and users

LBNL Laboratory Test Method

- **Principles:** Laboratory testing to obtain accurate measurements under various operating conditions
- **Device Layout:** The FFU to be tested will be mounted horizontally or vertically on the exit of the air chamber
- **Control and Method:** Use an ancillary fan and a damper to control the airflow rate across the FFU tested
- **Instrumentation:** Unit airflow rate;[5] total power usage; static (and total) pressure across the FFU

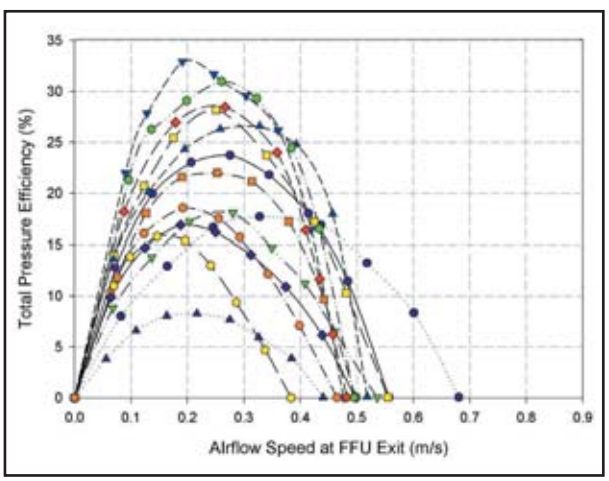

Figure 1. 4-feet by 2-feet FFU total pressure efficiency vs. airflow speed at FFU exit

Total Pressure (Power) Efficiency

Total Pressure (Power) Efficiency is the ratio of airflow velocity power to total electric power input to an FFU; a higher value indicates higher operating efficiency. Figure 1 shows total pressure efficiency curves of individual 4-feet by 2-feet FFUs as a function of airflow speeds at the FFU exit. The total pressure efficiency of one unit could be two-to-three-times as much as others at a typical test condition. The best efficiency of these FFUs at

an airflow speed of, say, 0.40 m/s, is around 25%, which is not surprisingly lower than that of a regular industrial fan with approximately the same capacity. On the other hand, the majority of the 4-feet by 2-feet units tested in this study were able to produce airflow within the range of 0.30 and 0.50 m/s, which is common in cleanroom applications, at a static pressure of about 100 Pa (or about 0.4 inch water).[3]

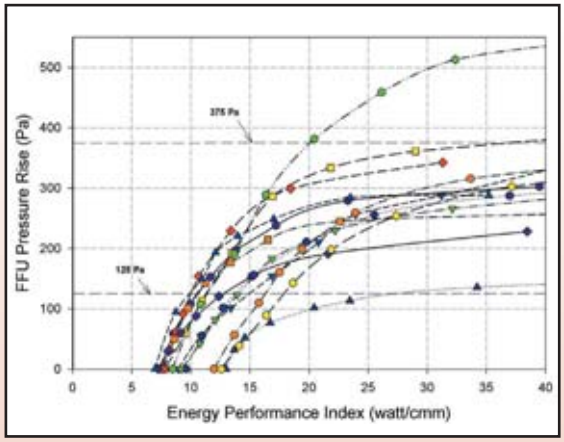

Figure 2. 4-feet by 2-feet FFU pressure rise vs. EPI

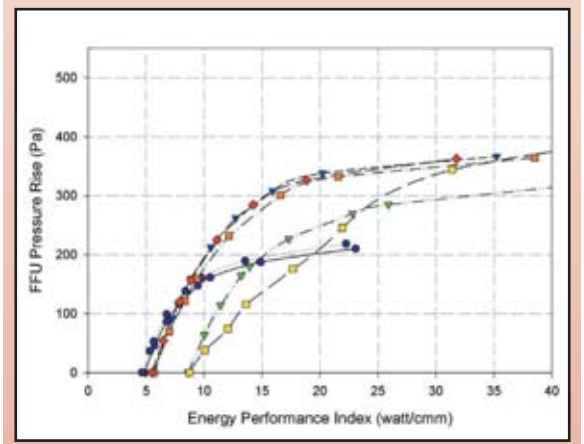

Figure 3. 4-feet by 4-feet FFU pressure rise vs. EPI

Energy Performance Index

Energy Performance Index (EPI) is the unit's total power usage normalized by the actual airflow rate through the FFU under certain conditions; a lower value indicates a better capability of delivering more airflow through the FFU supplied by the same level of electric power. Figure 2 shows the EPI values for the thirteen 4 feet x 2 feet FFUs. The median value of the performance index at 125 Pa (or about 0.5 inch water) is approximately 11.3 W per m^3/min (or 0.32 W/cfm), meaning that 50% of the FFUs tested perform better than 11.3 W per m^3/min (or 0.32 W/cfm). Figure 3 shows the EPI of 4-feet by 4-feet FFUs at 125 Pa falls in the range of 7.5 watts per m^3/min (or 0.21 W/cfm) to 13.5 watts per m^3/min (or 0.38 W/cfm), with the median value of less than 8.0 watts per m^3/min (or 0.23 W/cfm), which is lower (more efficient) than that of the 4-feet by 2-feet FFUs (11.3 watts per m^3/min, or 0.32 W/cfm). Depending on the operating conditions, the EPI values of an FFU can vary widely. This indicates that there is potential for many of the FFU suppliers to improve FFU energy performance. In the meantime, users will have opportunities to select more efficient units as a means of improving the performance of their cleanroom systems.

Summary

The laboratory test method developed by LBNL[2] applies specifically to evaluating fan filter units' energy and air movement performance in a laboratory setting. It does not include other performance metrics such as sound, vibration, filtration efficiency, outlet flow uniformity, or in situ performance. These are nonetheless important to overall FFU performance; and some of these are covered in relevant standards, certification documents, or recommended practices.[6,7,8] Currently the procedure is available for public review.

Laboratory testing of FFU energy performance provides useful data for suppliers and end users to understand the performance of FFU products. Significant benefits are expected by having such a method in place and specified by a majority of users. Where FFU applications are required, having comparable information on FFU energy performance would enable selection of more efficient units to improve energy efficiency, while maintaining and improving contamination control. For instance, using such a standard method for testing and reporting the energy performance of fan filter units, suppliers, users, and designers can make informed decisions to design and select more energy efficient models when FFUs are required. Market transformation toward energy efficient cleanroom systems could be accelerated through utility incentive programs based upon measured performance data. Utilities and other public interest programs promoting energy efficiency may be able to encourage use of more energy efficient models. Implementing such energy incentive programs will lead to large energy savings in buildings that required FFUs, such as cleanrooms, hospitals, and even post offices. Another ripple effect would be that suppliers would be encouraged to pursue innovative FFU designs that are more energy efficient. In addition, LBNL is collaborating with IEST in developing a new, more comprehensive FFU recommended practice guideline for industry use. Currently the IEST Working Group 36 (WG36) is planning to integrate the LBNL laboratory testing method into its RP development.

Looking forward to the next steps, future R&D efforts would include: 1) conducting tests of additional FFUs of various types, with different controls, and different designs; 2) improving FFU designs through investigating additional factors contributing to actual performance levels, such as motor types, and fan wheel design; 3) establishing an industry recommended practice guideline and developing an international standard; and 4) examining the applicability of efficient FFUs in contamination control in a wider market such as hospitals and even post offices.

Acknowledgement

This article is base upon a summary of two recent papers published by The Institute of Environmental Sciences and Technology (IEST)[3] and Semiconductor Equipment and Materials International (SEMI).[4] The project is funded by the California Energy Commission's Industrial section of the Public Interest Energy Research (PIER) program (http://www.energy.ca.gov/). This work was supported by the Assistant Secretary for Energy Efficiency and Renewable Energy, Office of Building Technology, State, and Community Programs, of the U.S. Department of Energy under Contract No. DE-AC03-76SF00098.

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BIOPHEX 2004

product showcase

Drainable Angle Fittings

New drainable angle fittings provide smooth flow and help configure biopharm process systems that are easy to drain and clean. Available in sizes 1/2 to 4 inches with elbow fittings in 88° and 92° bends; an 88° tee is also available. Other features include: heat traceable 316L materials; choice of clamps/connections; and vacuum annealed, tubular fittings. **SWAGELOK** Circle #81 on Free Product Information Card.

Sterile Alcohol Solution and Wipes

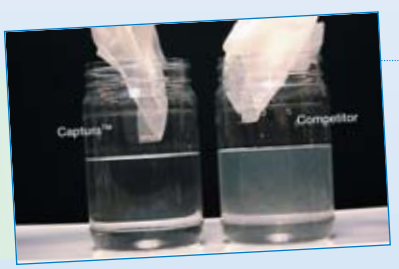
CiDehol ST Wipes are sterile wipes that are pre-saturated with 70% isopropyl alcohol for use in cleanrooms and sterile areas. Each pack is a convenient, re-sealable dispensing pouch containing 30 durable wipes. Each pack is double-bagged, gamma-irradiated via ANSI/ISO/AAMI American National Standards. A Lot Specific Document, detailing QC, irradiation and sterility, is shipped with each case. **DECON** Circle #82 on Free Product Information Card.

Crystal Scope

The Canty Crystal Scope can be used to collect valuable process information that is visually verifiable. Data such as particle count and density of the crystals is continually processed as well as the size and shape. Features a fused glass front cap and patented fiber optic cold lighting. **CANTY** Circle #83 on Free Product Information Card.

Cleanroom Garment Catalog

The in-stock cleanroom garment catalog from Prudential features their in-stock reusable cleanroom apparel, a glossary of terms and definitions relating to contamination control environments, the latest ISO Global Cleanroom Standards Primer, and cleanroom gowning and de-gowning procedures. **PRUDENTIAL CLEANROOM SERVICES** Circle #84 on Free Product Information Card.



Cleanroom Wipers and Mops

Anticon® introduces The Captura™ family of products (by Milliken) for sorbency and cleanliness. Captura™ is also available sterile as well as pre-moistened with various cleaning solutions. **MILLIKEN** Circle #85 on Free Product Information Card.

Magnetically Driven Mixer

The magnetically driven Sterimixer® provides efficient mixing while eliminating many potential sources of contamination. The mixer consists of the impeller, bearing, weld plate, drive unit, and control box. Available for vessel volumes ranging from 5 to 30,000 liters and viscosities up to 1000cP. Certified in accordance with ISO 9001 and other relevant industry standards. **ROPLAN** Circle #86 on Free Product Information Card.

2004 PRODUCT SHOWCASE

Powder Containment System

The Top Mount Bulk Powder Containment System makes potent powder handling safe and easy. Features include: fan/filtration system; turbulence-free airflow; enough room for larger balances on the base of the unit; cutout to accommodate the drum; multiple filtering options; face velocity alarm; and two port cutouts for waste disposal chutes. **FLOW SCIENCES** Circle #87 on Free Product Information Card.

Cleanroom Wipers

KIMTECH PURE* CL4 and CL5 critical task wipers for surface wiping in cleanroom environments can both be autoclaved and ETO-sterilized. The line of CL4 Wipers are resistant to acids, bases, and solvents, includes a pre-saturated alcohol wipe, and are available in sizes 4x4 inches, 9x9 inches, and 11.5x12 inches. The CL5 wipers have a high water absorbency rate, available in sizes 4x4 inches, 8x8 inches, and 12x12 inches. **KIMBERLY-CLARK PROFESSIONAL** Circle #88 on Free Product Information Card.

Integrated Systems

Services include integrated solutions, customized project design and flexibility, quality design and fabrication for custom and pre-engineered control cabinets, handling and assembly units, and custom assemblies. **FESTO** Circle #89 on Free Product Information Card.

Pipe and Tubing Hangers

The hangers are made in three basic designs: floor, ceiling, or wall mount. Features include: a rounded geometry without sharp corners, edges, and exposed threads; eliminates flat areas for dust or debris; compatible with pitched pipe runs; and hanger length made to order. **PBM** Circle #90 on Free Product Information Card.

Modular Cleanrooms

Modular cleanrooms of Class 10 to Class 100,000 facilities for Flowstar's Nova, Pulsar, Evolution and Galaxy series systems. Flowstar also provides turnkey custom cleanrooms and manufactures cleanroom workstations, tables, and laminar flowhoods. **FLOWSTAR** Circle #91 on Free Product Information Card.

Gas Flow Services

DH Instruments provides gas flow and pressure calibration standards and services including molbloc/molbox second generation fundamental mass flow calibration systems for high accuracy calibration and checking of MFSs and MFMs calibration system for CDGs. **DH INSTRUMENTS** Circle #92 on Free Product Information Card.

2004 PRODUCT SHOWCASE

PRODUCT FOCUS

CLEANROOM SERVICES

Cleanroom Certification
CIRCLE # 75

A. ***Cleanroom Certification.*** Air Filtration Management is an independent, NEBB certified firm specializing in testing and certification of cleanrooms and laminar flow HEPA filtered equipment. Trained technicians perform cleanroom certification in accordance with NEBB, IEST, and ISO standards. Individualized performance evaluations include precision filter integrity testing using robotic scans and filter challenges using PSL Spheres. Data is presented through advanced telecommunication transfers with AFM's headquarters. **AIR FILTRATION MANAGEMENT**

B. ***Technician Certification Program.*** Controlled Contamination Services now offers the Contamination Control Technician Certification Program. The program is being implemented with the intention of maintaining standards symbiotic with the continually changing technologies and requirements. The program is aligned with ISO and standards being generated by the Institute of Environmental Sciences and Technologies. **CONTROLLED CONTAMINATION SERVICES**

Technician Certification Program
CIRCLE # 76

C. ***Cleanroom Services.*** ACM offers services in certification (HEPA/ULPA filter supply and installation), microcleaning (cleaning and disinfecting cleanrooms), microbial testing (for air and surfaces), cleanroom classes (protocol training), and build clean protocol (supplies, training, monitoring, inspections, laundry, cleaning and certification). **ACM**

Cleanroom Services
CIRCLE # 77

D. ***Test Plant.*** The Model M pilot plant is a laboratory-scale test plant designed for feasibility testing of cross-flow membrane filtration applications in the microfiltration, ultrafiltration, and nanofiltration ranges. The unit can be set up for evaluation of a variety of membrane formats. Other features include compact and flexible modular design, and availability in customizable designs. Available for purchase or short-term lease. **GEA FILTRATION**

Test Plant
CIRCLE # 78

Turnkey Construction
CIRCLE # 79

E. ***Turnkey Construction.*** Clean Air Technology, Inc. is a "design and build" cleanroom contractor specializing in turnkey construction of modular Class 1 to Class 100,000 and ISO equivalent cleanrooms, and P3 Bio-Hazard containment facilities. Cleanrooms feature pre-fabricated modular, wall and top deck systems. **CLEAN AIR TECHNOLOGY**

F. ***Construction Services.*** J.M. Coull, Inc. provides Construction Management, Pre-Construction, General Contracting Services, and can provide Design-Build programming and design with any project. Over the last 20 years JMC has served a wide range of commercial and industrial clients including the life science and high-technology industries with new building projects, renovations and process retrofits. **J.M. COULL**

Construction Services
CIRCLE # 80

HOW it works

"DRY FOG" CLEANROOM DISINFECTION

Cleanroom disinfection is a routine process in many pharmaceutical, biotech, and cosmetic industries. Procedures for regularly wiping surfaces are often complemented by periodic aerosol-based disinfections. The chemicals used can range from sodium hypochlorite (bleach) to quaternary ammonia to phenols to formaldehyde-based chemicals. A normal procedure for cleanroom disinfection using formaldehyde can take two days or more.

Problem: **The corrosive nature of some of the chemicals and the time and special precautions needed to vent the rooms after disinfection.**

Solution: **An aerosol-based "dry fog" cleanroom disinfection system.**

Minncare Cold Sterilant is fully biodegradable and is less corrosive than other liquids, as has been shown in independent materials testing. It can be used for surface disinfection (wiping process) and/or for aerosol-based cleanroom disinfection using the new Minncare Dry Fog system introduced to European markets in 2003 and now approved for use in the US. The autoclavable Minncare Dry Fog system produces a fog of ultrafine droplets of precisely 7.5 microns diameter. The droplets bounce off of surfaces without wetting them (dry fog), and the vapor phase Minncare disperses rapidly and effectively throughout the room. The dispersion can reach even hard to access areas like those under tables or behind equipment. The system operates on compressed air and needs no electricity. The dry fog system is most effective when the system disperses a solution of Minncare Cold Sterilant and water into a room such that the room relative humidity is held at 80% to 90%. This optimizes the level of disinfectant in vapor phase as well as preventing condensation on surfaces that will slow the process. The company provides simple methods of determining the solution mix and volume that will be most effective and efficient in delivering the right amount of chemical and humidity to the cleanroom. At the end of the process, the Renatest® vapor detection system of calibrated tubes is used to measure any residual levels of hydrogen peroxide or peracetic acid in the room.

The total process time using this combination is extremely short: between two and five hours for cleanrooms up to 35,000 cubic feet including venting time (even when divided in multiple rooms) using a single Minncare Dry Fog system. Typical test results show that the Minncare Dry Fog system produces high level disinfection in a very short time period without leaving chemical residuals on surfaces.

The Minncare Dry Fog system has proved to be a very effective and safe system for aerosol-based disinfection of cleanrooms. Adapted to volumes up to 35,000 cubic feet, it can effectively replace existing chemical-based systems, providing substantial savings in time and cost, as well as a reduction in risk from toxic chemicals.

If you have an innovative product that solves a problem and you would like to see it featured in "How It Works," please send your information –in the above format– to Chris Janson at cjanson@a2c2.com with "How It Works" in the subject line.

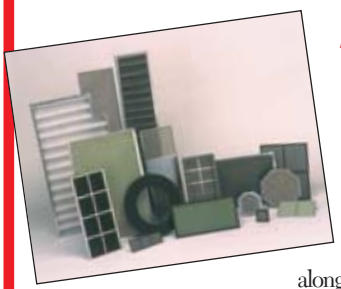
▲ **Circle No. 70 on Free Product Info. Card**

PRODUCT NEWS

Software Package

StarTalk XP for Windows® is a software package that directs the Flowserve StarPac® which uses sensors mounted on a valve body to measure flow. Features include: a single, simplified screen; expanded help files; enhance signature analysis; diagnostic checks; graphical PID (proportional integral derivative) control; tuning screen to configure variables; alarm explanations; configurable security setup; and virtual register support. **Flowserve Circle #93 on Free Product Information Card.**

Air Filters



Tough Air Filters protect electronic components that depend on forced air thermal management to keep them cool and functioning. The filters optimize reliable forced air thermal management and can provide EMI/RFI shielding along with particulate protection for electronics equipment used in both indoor and outdoor environments. **Universal Air Filter Circle #94 on Free Product Information Card.**

Modular Hardwall Cleanrooms

Clean Air Products introduces the Series 558 Vertical Flow Hardwall Modular Cleanrooms, available in Class 100 to Class 10. Each unit includes full-ceiling HEPA filter coverage, sidewall blower cabinets, and sidewall panels containing start/disconnect, wall receptacles, prefilters, and option cooling coils. Units are belt-driven, three-phase, and available in multiple voltages. Also come with other optional features. **Clean Air Products Circle #95 on Free Product Information Card.**

Fume Hood

The LabHood 20 is a fume hood featuring a sliding front sash, low airflow alarm (both visual and audible), a two speed fan, and integral lighting. The hood is shipped fully assembled and is multi-mode (it can be operated in ductless or both filter/vented mode). Available in two - six foot versions. **Air Science Technologies Circle #96 on Free Product Information Card.**

Turbo Pump

The TPH 1201 turbo pump contains a combination of high pumping speed for light gasses and high throughput for heavy gases. This 1200 l/s pump includes a rotor geometry that permits a high foreline tolerance of 0.5mbar. MTTP of over 250,000 hours can be expected. **Pfeiffer Vacuum Circle #97 on Free Product Information Card.**

IN THE NEWS

Intercept Technology Expands The Intercept Technology Group (ITG) Inc. formally admitted three new companies into its organization recently. These three companies are RJ Hanlon Company, Inc. of Cicero, IN; Tec-Hub Pte Ltd. of Singapore; and COMPTrade GmbH of Germany. Their addition to the ITG helps bring the benefits of Intercept Technology™ to an increasingly global audience. Intercept Technology is a multi-functional, fourth generation anti-corrosive, electro-static discharge protective packaging system - invaluable for today's micro-electronics and mixed metallic and organic constructions.

New White Paper on Cleanroom Garments CleanFit Systems of Portland, Oregon has published a new white paper, titled The Dirty Dozen: 12 ways to cut the expense, time, and stress of cleanroom garment systems. The paper addresses issues frequently encountered with cleanroom garment programs, including operating cost-effective cleanroom garment programs. CleanFit Systems audits cleanroom garment systems and implements gowning programs. For more information, visit www.cleanfitsystems.com.

PharmaSys Expands Westward; Hires Vice President PharmaSys, Inc. of Cary, N.C., has established a new region designed to serve clients in the western United States and Asia Pacific. The new western region has offices in Boise, Idaho and Boulder, Colorado. Phillip Martin has been hired as Vice President, Western US & Asia Pacific. He is responsible for operations in these regions and strengthening PharmaSys' position in the compliance and validation service market. Martin was most recently Director of International Corporate Affairs at Micron Technology, Inc.

Praxair Expands Advanced Components Manufacturing Praxair Electronics of Danbury, CT, has upgraded four of its Advanced Components facilities in North America. It now can offer the semiconductor industry improved tool-manufacturing processes by serving as an integrated supplier for the complete fabrication of critical chamber components for both 200mm and 300 mm geometries. The upgraded facilities are in Poughkeepsie, NY, Seattle, WA, Phoenix, AZ, and Houston, TX.

M+W Zander Expands in New York State M+W Zander, a firm specializing in the architectural and engineering design of cleanroom and production facilities, has expanded its presence in upstate New York through the opening of a new, full-service office, financial commitment to the Construction Trades Training Center design and construction services at the Watervliet Arsenal, and continued involvement with the Albany Nanotech at SUNY.

To submit your company news for consideration, please send your information –in the above format– to Chris Janson at cjanson@a2c2.com with "In The News" in the subject line.

PENCIL IT IN . . .

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BIOMEQ 2004, Philadelphia, PA.
Details: Frank Manley, 230-525-0675, fmanley@bioq.com or www.biomeq.com

September 19-23, 2004:
EOS/ESD Symposium and Exhibits, Grapevine (Dallas), TX.
Details: www.esda.org

September 20-22, 2004:
DISKCON USA, Santa Clara, CA.
Details: www.idema.org

September 20-23, 2004:
Chips to Hits® 2004, Seaport World Trade Center, Boston, MA.
Details: kchaudhuri@ibcusa.com

September 20-24, 2004:
PDA/FDA Joint Regulatory Conference, Washington, DC.
Details: www.pda.org

September 27-October 1, 2004:
NEBB Cleanroom Seminar and Examinations, Tempe, AZ.
Details: www.nebb.org.

September 28-30, 2004:
BIOPHEX 2004, San Francisco, CA.
Details: www.biophex.com

October 4-6, 2004:
3rd International Surface Cleaning Workshop and Tutorials, Northeastern University, Boston, MA.
Details: www.cmc.neu.edu

October 5-7, 2004:
Random Vibration and Shock Testing Training, Littleton, MA.
Details: www.equipment-reliability.com

October 7-8, 2004:
14th International Activated Carbon Conference, Pittsburgh, PA.
Details: www.pacslab.com

October 24-28, 2004:
2004 ISPE Annual Meeting, San Antonio, TX.
Details: www.ispe.org

November 3-4, 2004:
BIOMEQ 2004, Raleigh, NC.
Details: www.biomeq.com

November 7-11, 2004:
IEST Fall Conference, Annapolis, MD.
Details: www.iest.org

November 14-17, 2004:
Pharmaceutical Regulatory and Compliance Congress, Washington, D.C.
Details: www.PharmaCongress.com

April 7-8, 2005:
TurnKey Conference,
San Diego Marriott Hotel and Marina,
San Diego, CA.
Details: www.a2c2.com

Laboratory Table Top Homogenizer

The Pharma NS1001L, a tabletop model for the processing of biochemicals and pharmaceuticals, has the ability to process small volumes of liquids and pumpable fluids. Features include the ability to handle feeds at high viscosity, a compact design, FDA approved gaskets, and has no need for cooling/lubrication water. **Niro Circle #98 on Free Product Information Card.**

Recirculating Chillers

PolyScience 6000 Series Chillers provide protection for precision devices. Features include one-touch temperature control, high and low temperature alarms, pressure and flow rate alarms, and ambient temperature tracking capability. The chillers alert users instantly when process parameters such as fluid temperature, pressure, and rate, or ambient temperature fall outside user-set limits. **PolyScience Circle #99 on Free Product Information Card.**

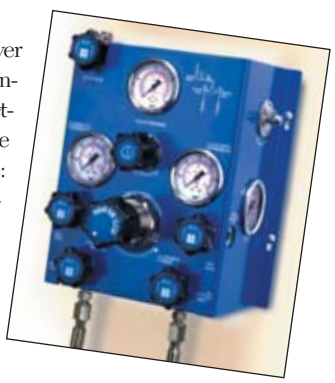
Optical Tables

Vibration Damping Optical Tables provide flat, stiff, highly damped surfaces with natural frequencies and can be customized for a variety of applications. Tables are offered in sizes up to 6x20 feet, and available in a range of thickness from 8-36 inches. Features include laser ports, shelves, tabletop enclosures, retractable casters, and modular butt splices for joining tables. **Kinetic Systems Circle #100 on Free Product Information Card.**

Amplifier

The AB5 amplifier supports all of Nanomotion's precision servo motors. By "linearizing" the voltage to velocity profile at the amplifier level, the AB5 eliminates the need for custom servo algorithms. Also features the option to turn on or off the motor static holding force. **Nanomotion Circle #101 on Free Product Information Card.**

Liquid ChangeOver System



The Model 8404L Liquid ChangeOver Regulator System provides constant, uninterrupted flow of specialty gases by directing flow from two separate dewars to the point of use. Other features include: scheduled dewar change-outs, a "Gas-Saver" circuit, adjustable delivery pressure, purge vent in the rear of the unit, and check valves on the inlet of the model. **Scott Specialty Gases Circle #102 on Free Product Information Card.**

WEB DIRECTORY

Regulatory Focus:

A Tale of Two Guidance Documents

ELAINE KOPIS SARTAIN

Guidance for Industry Sterile Drug Products Produced by Aseptic Processing Current Good Manufacturing Practice 1987 vs. 2003

The new draft "aseptic guideline," as it is often referred to in this industry, was initially released for industry feedback in 2002 by the Food and Drug Administration (FDA) as a concept paper. It was later discussed at a meeting of the Advisory Committee for Pharmaceutical Sciences, and was subsequently influenced by a Product Quality Research Institute working group comprised of 41 aseptic processing experts from varied industrial, academic, and regulatory backgrounds. The FDA's objectives in revising the 1987 guidance document are to provide greater clarity and to better reflect *current* manufacturing practices and capabilities.

Posted in September of 2003 for public commentary, this draft guidance document has several key differences from the 1987 version. The differences are focused in the following areas: cleanroom design; personnel; process design; quality control; environmental monitoring; and production records. This article will focus on two of these areas—cleanroom design, and personnel training, qualification, and monitoring.

Cleanroom Design

Although the 2003 draft guidance document contains many differences from the 1987 guide, including additional recommendations for clean air classifications for particulate and microbes, air velocity, and pressure differential, arguably the most significant difference is that the current draft includes a section on cleanroom design.

The 2003 draft guidance document seeks to capture elements of cleanroom management that we in the industry have long acknowledged. Specifically, the more traffic there is in, or immediately proximal to, the core manufacturing area, the higher the operational risk. The 2003 draft guidance document addresses the need to optimize personnel and material flow, to minimize the number of personnel and the number of interventions or transfers, and to add automation (for example, online weight checks, sterilize-in-place functions, and robotics) to further reduce the risk to the product. It also addresses cleanroom design and construction from a cleaning and sanitization perspective. For example, it recommends selecting seamless flooring and eliminating unnecessary equipment and fixtures, including floor drains.

There are detractors who may argue that the 2003 draft guidance document goes too far because it does not allow for the possibility that an aseptic operation without these elements can be successfully managed. If one views the 2003 draft guidance document as prescriptive, it may place a significant burden on some manufacturers who are already capable of producing sterile product. Although it is true that a "one size fits all" approach inevitably leaves some on the outside looking in, it is my view that these newer cleanroom design recommendations are sound and will improve the likelihood of manufacturing a sterile product.

Personnel Training, Qualification, and Monitoring

One of the most striking omissions of the 1987 guide is the lack of focus on the impact of personnel on the aseptic process. It is widely acknowledged that "people" are the chief contributors of contamination in the processing environment. Minimizing the risk from both thoughtless and deliberate personnel behaviors requires training and supervision.

The 2003 draft guidance document emphasizes training in aseptic technique, cleanroom behavior, microbiology, hygiene, gowning, patient safety hazard posed by nonsterile products, and specific, written standard operating procedures governing the operation. Additionally, the document recommends ongoing training and evaluation by qualified supervisors to determine that operators are conforming to all requirements, and stipulates that quality control professionals should provide oversight. Training is recommended for both operations personnel and laboratory personnel who are responsible for sampling in the area.

Gowning qualification is determined through post-gowning microbiological sampling. In the 2003 draft guidance document, re-qualification is recommended semi-annually, or yearly for automated operations with minimal personnel intervention. Routine glove monitoring is required since the stated goal for manufacturing is to have contamination-free gloves throughout the process. The 2003 draft guidance document stipulates that an investigation should be initiated whenever an operator exceeds established levels or shows an adverse trend.

Overall, the 2003 draft guidance document provides more input into the aseptic process than the 1987 version, including a clear bias toward more automation and less personnel involvement. Some may find this approach too limiting. Others will appreciate the codification of the practices they already employ. However, as with all FDA guidance documents, alternative approaches may be justified if there is a sound scientific basis.

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PREVENTING AND MEASURING CONTAMINATION IN AND OUT OF THE CLEANROOM

MEMS, NEMS, AND CONTAMINATION AT THE ATOMIC SCALE

BARBARA KANEGSBERG AND ED KANEGSBERG

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As electronic and mechanical sensors become microscopic, our world-view of contamination issues has to adjust. A few years ago, MEMS was a catchword. MEMS, or Micro-Electro-Mechanical Systems, combines mechanical elements, sensors, actuators, and electronics on a common silicon substrate. The technology is already used for pressure sensors, accelerometers and more. In a recent column, we discussed a SAW contamination surface film detector based on MEMS technology.[1]

More recently, the term NEMS has been introduced, with the "Micro" becoming "Nano." These smaller devices have the promise of even greater sensitivity, and much lower power consumption. As detection sensitivity increases, an array of new or rarely used words are likely to become commonplace. Milli-, micro-, and nano- prefixes are being joined by atto- (10^{-18}), zepto- (10^{-21}), and yocto- (10^{-24}). NEMS-based mass sensors have been proposed as part of a toolkit to be used for the inexpensive real-time analysis or detection of toxics or explosives. Protein molecules or viruses could be distinguished from one another by weight or by the affinity for a particular surface (e.g. body-antibody).[2]

Nanotribology takes the study of friction and adhesion and lubrication down to the molecular or atomic level. New contamination sensors, which are sensitive to extremely small quantities (including a balance with potential to weigh a single atom!), are under development. We will discuss some of these new sensors in greater detail next month.

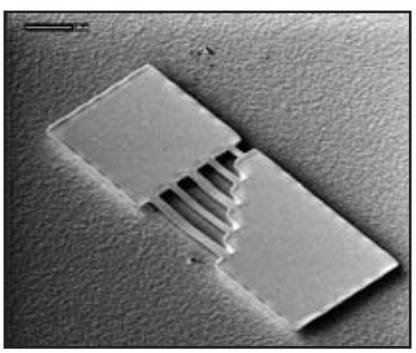

Figure 1. Single crystal Si microbridges with lengths from 1 µm to a little over 10 µm. The thickness of these microbridges is less than 50 nm. Photo courtesy of Dr. Panos Datskos, ORNL.

An inherent consequence of the expected trend toward NEMS-based devices will be increased significance of surface attributes including cleanliness, potential contamination sources, and surface quality or surface attributes. As dimensions decrease, the surface-to-volume ratio increases. At the ultimate limit one could envision a situation where the entire device is a monolayer surface with an analogous power and delicacy that biologists recognize in membrane structures.

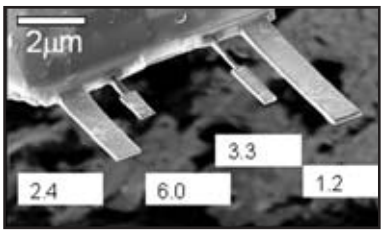

Figure 2. Electron micrograph of Si microcantilevers with resonance frequencies in the range of 1 to 10 MHz. Approximate values of the resonance frequencies are indicated. Photo courtesy of Dr. Panos Datskos, ORNL.

In such situations, surface contamination is an inherently important issue. Along the same line of thought, contamination particles that may be insignificant specks on a larger device may be virtual boulders on a NEMS device. Microscopy reveals that even the smoothest surface has roughness or structure at high magnification. Both MEMS and NEMS involve both structural and mechanical aspects, either rotating parts or vibrating parts. Contaminating particles can interfere with mechanical motion either by physical constraint (a microscopic "shoe in the door") or by changing balance conditions and degrading (or shifting) vibration resonances.

Another consequence of the higher surface-to-volume ratio is that the device physics is more dominated by surface effects than bulk effects. NEMS devices may have a substantial fraction of the total atoms at or near the surface.[3] At this point, mechanical aspects such as tensile strength change from bulk effects to surface effects. Particles or thin films, such as deposited from airborne molecular contamination,[4] can interfere with surface physics effects. MEMS or NEMS developers face some of the same cleanliness issues as those in wafer fabrication, with the added complication that most of the mechanical devices are not planar, making it harder to reach all surfaces. Since in some cases it has been demonstrated that supposed surface contamination can be actually a positive surface attribute,[5] one can envision the possibility of "contamination" used as a protective measure on microscopic devices.

Note: Thanks to Dr. Panos Datskos, Research Staff Member at Oak Ridge National Laboratory and a Research Associate Professor at the University of Tennessee, for his helpful contributions to and review of this column.

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Managing Safety with Hazard Rating Systems — Part II

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In today's litigious environment, the selection of cleaning chemicals and instruction for their use are not as simple as repeating what has been done before. Management of workplace and environmental safety requires quantitative evaluation of alternatives, development of safe procedures and process equipment, stewardship of products, and training of workers.

Hazard Rating Systems (HRSs) have been developed to meet these four needs, and others. Their use is mandated by entities whose span of control includes governments and individual laboratories. The common (in the US) National Fire Protection Association (NFPA) scheme, the risk and safety phrase systems used in the EC and UK, and the EPA-sponsored Indiana Relative Chemical Hazard Score (IRCHS) HRSs were covered in the July 2004 column. Other systems are described below.

Exposure Limit Probability

The cornerstone idea is that chemicals which have relatively low exposure limits for entry into the body by inhalation, and are quite non-volatile are safer to use than are chemicals with relatively higher exposure limits which are considerably more volatile. Said another way, it doesn't matter if it's hazardous if it doesn't evaporate.

This idea is advanced by chemical manufacturers whose products have low exposure limits for reasons other than that they present deadly hazard in use. For example, the exposure limit of benzene is 1 ppm; for dibasic acid ester solvents (DBE, etc.), it is 1.5 ppm. These exposure limits, taken alone, would suggest DBE is as lethal as benzene. But, the two hazards are not comparable—benzene is a carcinogen, while DBE reversibly irritates one's nose!

The Vapor Hazard Ratio (VHR) HRS is the dimensionless ratio of equilibrium vapor phase concentration divided by the use temperature divided by the exposure limit. The VHR for DBE is 87. That for IPA is 103. And that for benzene is more than 1,000. A variation of this system is to multiply the VHR by either the NFPA flammability rating or the sum of all three NFPA ratings. VHR doesn't speak to protective action.

South African Paint Manufacturers

Their simple and intelligently thought out system reports only in terms of health hazards and what protective equipment should be used to protect against them.

Health hazards are ranked in a numerical system. Protective equipment to combat them is listed simply and clearly. The two are combined into the South African Paint Manufacturers Association (SAPMA) hazard ranking system.

There are four levels of health hazard: minimal (4); slight (3); moderate (2); and serious (1). Please note this order is inverse to the NFPA system—there is negligible standardization among HRSs. Nine types of protective schemes are covered, ranging from nothing specific (A) to gloves and safety goggles (C) to "consult your supervisor" (K). The rating is a combination of number and letter. The rating 2E (or 2 HE) means moderate risk requiring gloves, safety goggles, and a gas respirator.

SAPMA does not publish a list of chemicals with their ratings; users are expected to classify them. I see this as a strong positive in that those who need to know are part of the hazard classification process. The SAPMA HRS is seriously flawed in that it is limited to health hazards only (flammability or reactivity for example). But, unlike EINECS and CHIPS, it is incredibly easy to communicate.

A Preferred System

This is preferred by absolutely no one except your author, because it has never before been published. Often the best advice is to steal shamelessly from the best. My preferred system has that heritage.

I suggest morphing the simplicity and breadth of the NFPA HRS (which doesn't speak to protective procedures or equipment) into the SAPMA HRS (which does speak to protective issues but is limited in focus to health issues).

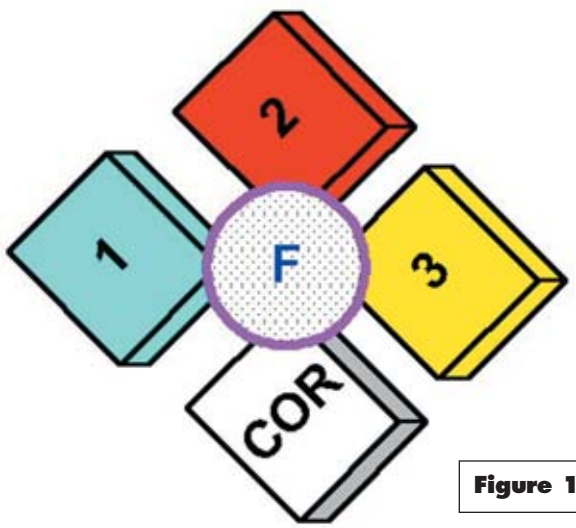

Figure 1

The "four diamond" image would be modified (Figure 1) with a centered symbol in which the code for protective equipment would be inserted. The values showing 1, 2, 3, and F are fictitious. But the preferred change is real: users would now receive simple guidance on the package label about the hazards of the chemical AND about protective equipment required for use with this chemical.

Summary

Hazard rating systems are tools to achieve ends; better choices with less risk and fewer incidents. Though the use of some is required by governments, the use of any HRS can be only a part of a hazard evaluation, process development, and training approach.

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